directed to an invention not patentably distinct from claims 1-14 of commonly assigned U.S. Patent No. 5,891,468.

Applicants respectfully traverse this rejection.

A. The Present Invention

Claims 71-81 of the present invention are directed to a liposome composition comprising a targeting conjugate. The targeting conjugate is comprised of (i) a lipid having a polar head group and a hydrophobic tail, (ii) a hydrophilic polymer having a proximal end and a distal end, said polymer is attached at its proximal end to the head group of the lipid, and (iii) a targeting ligand attached to the distal end of the polymer.

B. The 5,891,468 Patent

Claims 1-14 of the '468 patent are directed to a suspension of liposomes where at least a portion of the lipids are derivatized with a diblock copolymer comprised of a hydrophilic polymer and a hydrophobic polymer. The hydrophilic and hydrophobic polymers are joined by a bond effective to release the hydrophilic polymer (claim 1).

Claim 8 is directed to an embodiment where the hydrophilic polymer chains include a ligand for binding to a receptor on a target cell. Claim 9 calls out specific ligands, and claim 10 recites an embodiment where a ligand is directly attached to the lipid surface.

C. Analysis

M.P.E.P. § 804 states: "In determining whether a nonstatutory basis exists for a double-patenting rejection, the first question to be asked is - does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent? The question seeks to determine if the invention of the pending application is a mere variation

(which would have been obvious to those of ordinary skill in the art) of an already claimed invention."

The claims in the present invention are directed to a targeting conjugate comprised of a lipid, a polymer and a targeting ligand attached to the polymer.

In contrast, the closest claims in the '468 patent are directed to a liposome that includes a diblock copolymer composed of a lipid derivatized with a hydrophobic polymer attached to a hydrophilic polymer by a releasable chain and a ligand (claims 8-10).

To arrive at the present claims based on the claims in the '468 patent it would be necessary to (1) isolate the diblock copolymer from the liposome composition; (2) omit the hydrophobic polymer from the diblock copolymer; and (3) omit the releasable linkage between the hydrophobic and hydrophilic portions of the diblock copolymer. There is simply no guidance in the claims of the '468 patent for making these modifications.

Therefore, Applicants submit that the invention as presently claimed is patentably distinct from U.S. Patent No. 5,891,468. Applicants respectfully request withdrawal of the obviousness-type double patenting rejection.

II. Rejection under 35 U.S.C. §102

Claims 21-25, 60 and 71 were rejected under 35 U.S.C. §102(a) or (b) as allegedly being anticipated by Torchilin *et al.*, U.S. Patent No. 5,534,241. This rejection is respectfully traversed for the following reasons.

A. The Present Invention

The present invention describes targeting conjugates comprised of (i) a lipid having a polar head group and a hydrophobic tail; (ii) a hydrophilic polymer attached to the polar

head group of the lipid; and (iii) a targeting ligand attached to the distal end of the hydrophilic polymer. Also described is a liposome composition comprising the targeting conjugate.

B. The Cited Art

TORCHILIN ET AL. describe a polychelating compound for use in liposomes or micelles. The polychelating compound is comprised of (i) a lipid, (ii) a polymer; and (iii) metal-chelating agents linked to the side groups of the polymer (Col. 1, lines 40-48; Col. 2, lines 10-13). A micelle of the polychelating compound is described (Col. 2, lines 16-17).

Liposomes including the polychelating compound "may be modified with a targeting group, e.g., an antibody, bound to the membrane." (Col. 2, lines 20-23). As described on Col. 2, lines 33-38, a group is 'bound' to a liposome membrane when it is chemically or physically attached to the membrane, *e.g.*, by the intercalation of a lipid-soluble anchor into the membrane itself, or by binding directly to active groups of membrane lipids, thus using a preexisting anchor.

Thus, Torchilin *et al.* teach a lipid-polymer-metal chelator conjugate. Torchilin *et al.* teach liposomes including this conjugate and additionally including a targeting ligand attached to the bilayer membrane. Torchilin *et al.* fail to teach a lipid-polymer-targeting ligand conjugate.

C. Analysis

According to the M.P.E.P. § 2131, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference".

Torchilin *et al.* fail to teach a lipid-polymer-targeting ligand conjugate. As described above, Torchilin *et al.* teach a

lipid-polymer-metal chelator conjugate (Col. 1, lines 40-48 and Col. 2, lines 10-13). Liposomes containing this conjugate can be further modified with a targeting group, such as an antibody, by binding the targeting group to the lipid membrane surface of the liposome (Col. 2, lines 18-38). The liposomes of Torchilin *et al.* may further include a protective hydrophilic polymer bound to the liposome surface (Col. 2, lines 23-32).

Nowhere does Torchilin *et al.* teach a lipid-polymer-targeting ligand conjugate.

The Examiner appears to assert that the metal-chelating agent is a targeting ligand. The metal-chelating agent described by Torchilin *et al.* is a radio-contrast agent, such as gadolinium diethylenetriamine pentaacetic acid (DTPA), described by Tilcock *et al.*, cited at Col. 1, line 4 of Torchilin *et al.* (a copy of Tilcock *et al.* is enclosed herewith). Radio-contrast agents are quite different from the targeting ligand of the present invention, which interact with a cell or tissue receptor in the body, as is clear from the description of the targeting ligand beginning on page 22 of the specification.

Accordingly, because Torchilin *et al.* fails to describe a targeting conjugate comprised of a lipid, a polymer, and a targeting ligand, the standard for anticipation has not been met. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(b).

III. Rejections under 35 U.S.C. §103

Claims 21-32 and 57-81 were rejected under 35 U.S.C. §103 as allegedly obvious over Torchilin *et al.* further in view of Harris *et al.* (U.S. Patent No. 5,932,462).

A. The Present Invention

The present invention is described above.

B. The Cited Art

TORCHILIN ET AL. is described above.

HARRIS ET AL. describe a mono-functional polymer for coupling to a protein, lipid, or ligand. The polymer has a single reactive moiety ("moiety "Z" in the structure of the abstract and claim 1) and two nonpeptidic and nonreactive polymeric arms.

Because the polymer derivative has a single reactive site, the polymer derivative can be attached to a protein, a ligand or, a lipid. Thus, the teaching in Harris *et al.* is limited to a protein-polymer conjugate, or a lipid-polymer conjugate, or a ligand-polymer conjugate. Nowhere does Harris *et al.* describe a lipid-polymer-ligand conjugate.

C. Analysis

Applicants fail to understand how the combined teachings in the cited documents arrive at the claimed invention. Torchilin *et al.* describes a lipid-polymer-chelating agent conjugate. The chelating agent is a metal-chelator for use as a radio contrast agent in radioimaging procedures. Nowhere does Torchilin *et al.* show or suggest a lipid-polymer-targeting ligand conjugate, where the targeting ligand is one having activity with a cell or tissue receptor.

Harris *et al.* teaches a polymer derivative having a single reactive group for reaction with a protein, lipid or ligand. The polymer derivative in Harris *et al.* is designed to "mask" or "shield" the attached protein or lipid. In contrast, the targeting ligand in the present invention is attached to the polymer-lipid anchor in such a way to deliberately expose the ligand for interaction with its cell or tissue receptor.

Thus, it does not make sense to modify the teaching of Harris *et al.* to, for example, attach a ligand to the lipid-polymer

conjugate, since the sole purpose of the derivative in Harris *et al.* is to provide a masked or shielded ligand.

Further, it does not make sense to modify Torchilin *et al.* to include a protein ligand as taught by Harris *et al.* for at least two reasons. First, Harris *et al.* is concerned with masking or shielding the protein or ligand. There is no motivation in Harris *et al.* to attach the protein or ligand in such a way that it is exposed for interaction. Second, attaching the protein or ligand to the lipid-polymer-contrast-agent polychelator compound of Torchilin *et al.* requires substitution of the protein or ligand for the metal chelator. Such a substitution of a protein ligand for the metal-chelating agent of Torchilin *et al.* defeats the purpose of the invention in Torchilin *et al.* to provide a polychelating compound. There is simply no motivation in either Torchilin *et al.* or Harris *et al.* to make such a modification. To assert otherwise improperly relies on Applicants' own teaching.

Since the references alone or in combination fail to show or suggest a targeting conjugate comprised of (i) a lipid; (ii) a hydrophilic polymer; and (iii) a targeting ligand attached to the hydrophilic polymer, the present invention patentably defines over the cited documents. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

CONCLUSION

It is respectfully submitted that each of the pending claims 21-32 and 57-81 are in condition for allowance. A Notice of Allowance is respectfully requested.

The Examiner is invited to contact Applicants' representative at (650) 838-4410 if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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